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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants: Ray W. WOOD et al.

Title: NANOPARTICULATE BECLOMETHASONE COMPOSITIONS (AS AMENDED)

Appl. No.: 10/667,472

Filing Date: 09/23/2003

Examiner: Mina Haghighatian

Art Unit: 1616

Confirmation Number: 9063

BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants hereby petition the Commissioner under 37 C.F.R. § 1.136(a) for a one-month extension of time for response in the above-identified application for the period required to make the attached response timely. The extension fee for response within the first month is $120.00. Under the provisions of 37 C.F.R. § 41.37, this Appeal Brief is being filed together with a credit card payment form also including the amount of $500.00 covering the 37 C.F.R. 41.20(b)(2) fee for filing an Appeal Brief. If these fees are deemed to be insufficient, authorization is hereby given to charge any deficiency (or credit any balance) to our deposit account 19-0741.

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I. REAL PARTY IN INTEREST

The real party in interest is Elan Pharma International Limited.

II. RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any related appeal or interferences.

III. STATUS OF CLAIMS

Claims 1-9 are canceled and claims 10-74 are pending. Claims 23 and 27-74 are withdrawn, so claims 10-22 and 24-26 are under consideration, rejected, and appealed.

IV. STATUS OF AMENDMENTS

Appellants made no amendments after the Final Office Action mailed April 6, 2006. All amendments have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 10, the only independent claim involved in this appeal, claims a nanoparticulate beclomethasone dipropionate composition.[1] The composition includes beclomethasone dipropionate particles having an average particle size of less than about 1000 nm and at least one surface modifier.[2]

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[1] *See* Spec. at page 18, lines 18-20.

[2] *See* Spec. at 2, lines 25-28; 10, lines 24-25.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellants presents a single ground of rejection for consideration on appeal.[3] Specifically, Appellants present for consideration the rejection of claims 10-22 and 24-26 under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 5,145,684 to Liversidge *et al.* ("Liversidge") in view of Lacy *et al.*, DRUG INFORMATION HANDBOOK pp,. 95-96 (Lexi-Comp, Inc. 1993) ("DIH").

VII. ARGUMENT

Liversidge in view of DIH fails to render the claimed invention obvious for at least two reasons. First, there is no *prima facie* case of obviousness because there is no motivation to combine Liversidge and DIH. Moreover, given the disclosures of Liversidge and DIH, one of skill in the art would have no reasonable expectation of success in obtaining the claimed invention. The entire rejection is based on the rationale that Liversidge suggests nanoparticulate corticosteroid compositions, and based on this teaching, one of skill in the art would scour the literature for specific corticosteroids, such as beclomethasone, and formulate them into nanoparticulate active agent compositions. Such reasoning cannot adequately support the obviousness rejection. Second, any *prima facie* case of obviousness has been rebutted by showing unexpected results. Indeed, the claimed invention provides a nanoparticulate beclomethasone composition that provides a number of unexpected properties as compared to traditional beclomethasone composition.

[3] The Final Office Action mailed April 6, 2006, also set forth a number of double patenting rejections. However, Applicants submitted a terminal disclaimer on July 7, 2006, which obviated the double patenting rejections. See Appellants' reply filed July 7, 2006 at 15. Thus, these rejections are no longer at issue.

A. The Examiner Has Failed to Establish a Prima Facie Case of Obviousness

A *prima facie* case of obviousness requires three basic criteria to be met.[4] First, there must be some suggestion or motivation to modify the references or to combine reference teachings in such a way as to arrive at the claimed invention.[5] Second, one of skill in the art must have a reasonable expectation of success in combining or modifying the references in the way suggested.[6] Finally, the prior art references must teach or suggest all the claim limitations when combined.[7]

Here, there is no *prima facie* case of obviousness, because the appealed rejection fails to satisfy two of the basic criteria. First, there is no suggestion or motivation to modify the references in the manner argued by the Examiner. Second, given the disclosures of the two cited references, one of skill in the art would not have a reasonable expectation of success in modifying the references as suggested by Examiner. Thus, the obviousness rejection cannot be sustained.

1. The Prior Art Lacks Motivation To Combine Liversidge And DIH

Liversidge generally relates to nanoparticles of a crystalline drug substance with a surface modifier absorbed on the surface thereof. In that regard, Liversidge discloses a lengthy list of classes of drugs substances, such as corticosteroids, and examples of some particular drug substances, such as Steroid A, that could be used to form a nanoparticulate

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[4] *See* MPEP § 2142; *see also In re Vaeck*, 947 F.2d 488, 493, 20 USPQ.2d 1438, 1442 (Fed. Cir. 1991).

[5] *Id.*

[6] *Id.*

[7] *Id.*

active agent composition.[8] However, Liversidge makes no mention of beclomethasone dipropionate, nor are corticosteroids even a "preferred" class of drugs.[9]

The Examiner recognizes Liversidge's deficiency in failing to teach beclomethasone and turns to DIH to remedy this deficiency. According to the Examiner, one of skill in the art would turn to DIH, select beclomethasone, and use beclomethasone with the teachings of Liversidge for the following reason:

> It would have been obvious to a person of ordinary skill in the art at the time the invention was made, given the general formulations of Liversidge on formulations containing active agents including corticosteroids, to have looked in the art for other specific species of corticosteroids suitable for formation of compositions, as disclosed in Drug Information Handbook, with reasonable expectations of successfully preparing formulations comprising different active agents for treating different disorders.[10]

In other words, because Liversidge listed corticosteroids as a class of drugs from which "[s]uitable drug substances can be selected," a skilled artisan would search the literature and form nanoparticulate forms of <u>every</u> corticosteroid, including beclomethasone.

The purported motivation does not satisfy the requirement for a motivation to combine or modify because the rationale fails to provide motivation to select beclomethasone specifically from among the many corticosteroids. It is not enough for the prior art to disclose beclomethasone as a corticosteroid, because "[s]ome motivation to select the <u>claimed species</u> ... must be taught by the prior art."[11] *See also In re Deuel*, 51 F.3d at 1558-59, 34 USPQ2d 1210, 1215 ("No particular one of these DNAs can be obvious unless there is something in

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[8] Liversidge at col. 3, line 53 – col. 4, line 27.

[9] *Id.* at col. 4, lines 5-7.

[10] Office Action mailed October 11, 2005 at 4.

[11] MPEP § 2144.08(II)(A)(4)(a).

the prior art to lead to the particular DNA and indicate that it should be prepared"). This requirement that the motivation be specific to the recited species stems from the well-established tenet that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious...."[12]

Here, the prior art lacks such a motivation to select beclomethasone from among many corticosteroids. In fact, the Examiner offers no rationale to specifically select beclomethasone and relies entirely on the fact that "[o]ne of ordinary skill in the art is well versed that beclomethasone is a commonly and widely used steroid and would be able to choose beclamethasone as the glucocorticosteroid of Liversidge."[13] As discussed above, it is not enough that one of skill in the art "be able to choose" a specific species. There must be a motivation to select the species, and such motivation to arrive at the presently claimed invention is lacking.

2. One Of Skill In The Art Would Not Have A Reasonable Expectation Of Success In Combining Liversidge With DIH As Urged By The Examiner

One of skill in the art would not have a reasonable expectation of success in modifying Liversidge as argued by the Examiner, because Liversidge warns against indiscriminate selection of drugs. Specifically, Liversidge teaches that "not every combination of surface modifier and drug substance provides the desired results [of a stable nanoparticulate composition]."[14] This is due in part to the requirement that the surface modifier adsorb to the surface of the drug substance. Indeed, Liversidge teaches that "[t]he

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[12] MPEP § 2143.01(III); *see also In re Brouwer*, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996).

[13] Advisory Action mailed July 24, 2006 (emphasis added).

[14] Liversidge, col. 7, lines 21-23.

surface modifier is adsorbed on the surface of the drug substance in an amount sufficient to maintain an effective average particle size of less than about 400 nm."[15] The adsorption of the surface stabilizer to the drug substance is essential in the formation of stable nanoparticles. Thus, one of skill in the art would not have known *a priori* whether or not a surface stabilizer would adsorb to any particular drug, such as beclomethasone. Accordingly, there can be no reasonable expectation of success.

The absence of a reasonable expectation of success is underscored by Liversidge's comparative examples. While "[o]bviousness does not require absolute predictability of success," obviousness does require "a reasonable expectation of success,"[16] and "there can be little better evidence negating an expectation of success than actual reports of failure."[17] Liversidge's comparative examples provide precisely this type of evidence, because they confirm that selection of surface modifiers and drug substances is not a trivial endeavor and that some combinations fail to result in suitable compositions.[18] Such demonstrated failures deprive one of skill in the art from enjoying any reasonable expectation of success and offer, at best, a hope for success. Accordingly, the evidence of record militates against any finding of a reasonable expectation of success.

B. The Claimed Invention Results In Unexpected Results

"A *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior

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[15] Liversidge, col. 5, lines 13-15.

[16] *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

[17] *See, e.g.*, *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354, 65 USPQ.2d 1961, 1972 (Fed. Cir. 2003).

[18] *See* Liversidge, Comparative Examples A-F (cols. 14-15).

properties.[19] In this case, Appellants rebutted any *prima facie* case by showing unexpected results. Specifically, Example 1 of the specification describes the preparation of a nanoparticulate beclomethasone composition, as claimed, and compares it to a conventional beclomethasone composition.[20] The specification states that "only about 7% of the [beclomethasone] presented as a suspension or raw drug substance reaches the impactor."[21] On the other hand, "the use of nanoparticles led to a significantly higher fraction reaching the impactor."[22] In addition, a greater fraction of beclomethasone remained in the nebulizer when raw drug substance rather than the nanoparticulate form was used.[23] Thus, the experimental results demonstrate that the nanoparticulate form of beclomethasone results in less waste and more effective delivery. This result was not expected from the prior art and rebuts a *prima facie* case of obviousness.

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[19] *See* M.P.E.P. § 2144.09 (citing *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963)).

[20] Spec. at page 18, line 17 – page 24, line 4.

[21] Spec. at page 21, lines 27-28.

[22] *Id.* at page 21, lines 29-30.

[23] *See* Table II, col. 4 (page 23); spec. at page 21, lines 14-26.

VIII. Conclusion

The rejection of claims 10-22 and 24-26 under 35 U.S.C. § 103(a) as allegedly obvious over Liversidge in view of Lacy DIH is untenable because a *prima facie* case of obviousness has not been established. Indeed, the prior art lacks a motivation to arrive at the claimed invention, and the prior art belies any expectation of success. Even if a *prima facie* case of obviousness had been established, Appellants have rebutted that case by demonstrating unexpected results. Thus, Appellants respectfully request that the Examiner's rejection be reversed.

Respectfully submitted,

Date Oct 17, 2006

By _____

FOLEY & LARDNER LLP
Customer Number: 31049
Telephone: (202) 672-5538
Facsimile: (202) 672-5399

Michele M. Simkin
Attorney for Applicants
Registration No. 34,717

CLAIMS APPENDIX

Claims 1 – 9 (Cancelled).

10. (Previously Presented) A nanoparticulate composition comprising:

(a) beclomethasone dipropionate particles having an average particle size of less than about 1000 nm; and

(b) at least one surface modifier.

11. (Previously Presented) The composition of claim 10, wherein the effective average particle size of the beclomethasone dipropionate particles is less than about 1000 nm, meaning that at least 90% of the particles have a particle size of less than about 1000 nm.

12. (Previously Presented) The composition of claim 10, wherein the effective average particle size of the beclomethasone dipropionate particles is less than about 400 nm, meaning that at least 90% of the particles have a particle size of less than about 400 nm.

13. (Previously Presented) The composition of claim 10, wherein the effective average particle size of the beclomethasone dipropionate particles is less than about 300 nm, meaning that at least 90% of the particles have a particle size of less than about 300 nm.

14. (Previously Presented) The composition of claim 10, wherein the effective average particle size of the beclomethasone dipropionate particles is less than about 100 nm, meaning that at least 90% of the particles have a particle size of less than about 100 nm.

15. (Previously Presented) The composition of any of claims 11-14, wherein at least 95% of the beclomethasone dipropionate particles have a particle size less than the effective average.

16. (Previously Presented) The composition of any of claims 11-14, wherein at least 99% of the beclomethasone dipropionate particles have a particle size less than the effective average.

17. (Previously Presented) The composition of claim 10, wherein the surface modifier is present in an amount of from about 0.1% to about 90%, by weight, based on the total combined weight of the beclomethasone dipropionate and surface modifier.

18. (Previously Presented) The composition of claim 10, wherein the surface modifier is present in an amount of from about 0.1% to about 75%, by weight, based on the total combined weight of the beclomethasone dipropionate and surface modifier.

19. (Previously Presented) The composition of claim 10, wherein the surface modifier is present in an amount of from about 20% to about 60%, by weight, based on the total combined weight of the beclomethasone dipropionate and surface modifier.

20. (Previously Presented) The composition of claim 10 formulated as an aqueous dispersion.

21. (Previously Presented) The composition of claim 10 formulated as a dispersion in a liquid media selected from the group consisting of aqueous salt solutions, safflower oil, and a solvent.

22. (Previously Presented) The composition of claim 21, wherein the solvent is selected from the group consisting of ethanol, t-butanol, hexane, and glycol.

23. (Withdrawn) The composition of claim 10, formulated as a dry composition.

24. (Previously Presented) The composition of claim 10, comprising two or more surface modifiers.

25. (Previously Presented) The composition of claim 10, wherein the surface modifier is selected from the group consisting of nonionic and ionic surfactants.

26. (Previously Presented) The composition of claim 10, wherein the surface modifier is selected from the group consisting of gelatin, casein, lecithin, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxy propylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, tyloxapol, poloxamers, poloxamines, dextran, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonate, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)\text{-}CH_2(CHOH)_4(CH_2OH)_2$, decanoyl-N-methylglucamide, n-decyl-β-D-glucopyranoside, n-decyl-β-D-maltopyranoside, n-dodecyl-β-D-glucopyranoside, n-dodecyl-β-D-maltoside, heptanoyl-N-methylglucamide, n-heptyl-β-D-glucopyranoside, n-heptyl-β-D-thioglucoside, n-hexyl-β-D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl-β-D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl-β-D-glucopyranoside, octyl-β-D-thioglucopyranoside, p-isononylphenoxypoly(glycidol), dioctylsulfosuccinate (DOSS), glycerol, dodecyl trimethyl ammonium bromide, a charged phospholipid, the triblock copolymer B20-3800, and the triblock copolymer B20-5000.

27. (Withdrawn) The composition of claim 26, wherein the surface modifier is selected from the group consisting of block copolymers of ethylene oxide and propylene oxide, tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, a dioctyl ester of sodium sulfosuccinic acid, and dimyristoyl phophatidyl glycerol.

28. (Withdrawn) The composition of claim 10, wherein the surface modifier is polyvinyl alcohol.

29. (Withdrawn) A method of making a nanoparticulate beclomethasone dipropionate composition comprising contacting particles of beclomethasone dipropionate with at least one surface stabilizer for a time and under conditions to reduce the average particle size of the beclomethasone dipropionate particles to less than about 1000 nm.

30. (Withdrawn) The method of claim 29, comprising:

(a) dispersing particles of beclomethasone dipropionate in a liquid dispersion media in which the particles are poorly soluble; and

(b) applying mechanical means in the presence of grinding media to reduce the average particle size of beclomethasone dipropionate to less than about 1000 nm,

wherein the beclomethasone dipropionate particles are reduced in size in the presence of at least one surface modifier, or wherein at least one surface modifier is added to the liquid dispersion media following particle size reduction of beclomethasone dipropionate.

31. (Withdrawn) The method of claim 30, wherein the mechanical means is a dispersion mill.

32. (Withdrawn) The method of claim 31, wherein the dispersion mill is selected from the group consisting of a ball mill, an attritor mill, a vibratory mill, and a media mill.

33. (Withdrawn) The method of claim 29 or 30, wherein the time required to reduce the particle size of beclomethasone dipropionate is from about 1 minute up to about 5 days.

34. (Withdrawn) The method of claim 29 or 30, wherein the beclomethasone dipropionate particles are reduced in size at an ambient temperature.

35. (Withdrawn) The method of claim 29 or 30, wherein the beclomethasone dipropionate particles are reduced in size at a less than about of less than about 40°C.

36. (Withdrawn) The method of claim 30, wherein the grinding media is spherical in shape and has an average particle size of from about 0.1 mm to about 3 mm.

37. (Withdrawn) The method of claim 36, wherein the grinding media has an average particle size of from 0.2 mm to about 2 mm.

38. (Withdrawn) The method of claim 37, wherein the grinding media has an average particle size of from 0.25 mm to about 1 mm.

39. (Withdrawn) The method of claim 37, wherein the grinding media has an average particle size of from 0.25 mm to about 1 mm.

40. (Withdrawn) The method of claim 30, wherein the grinding media is spherical in shape and has an average particle size of less than about 75 microns.

41. (Withdrawn) The method of claim 30, wherein the grinding media has a density greater than about 3 g/cm^3.

42. (Withdrawn) The method of claim 30, wherein the grinding media comprises a compound selected from the group consisting of zirconium oxide, zirconium silicate, glass, stainless steel, titania, alumina, 95% ZrO_2 stabilized with yttrium, and polymeric resin grinding media.

43. (Withdrawn) The method of claim 42, wherein the grinding media comprises spherical particles consisting essentially of a polymeric resin.

44. (Withdrawn) The method of claim 42, wherein the grinding media comprises spherical particles comprising a core which is coated with a polymeric resin.

45. (Withdrawn) The method of claim 42, wherein the polymeric resin is selected from the group consisting of crosslinked polystyrenes, styrene copolymers, polycarbonates, polyacetals, vinyl chloride polymers, vinyl chloride copolymers, polyurethanes, polyamides, fluoropolymers, high density polyethylenes, polypropylenes, cellulose ethers, cellulose esters, polyhydroxymethacrylate, polyhydroxyethyl acrylate, and silicone containing polymers.

46. (Withdrawn) The method of claim 45, wherein the polymeric resin is selected from the group consisting of polystyrene crosslinked with divinylbenzene, poly(tetrafluoroethylenes), cellulose acetate, and polysiloxanes.

47. (Withdrawn) The method of claim 42, wherein the polymeric resin is biodegradable.

48. (Withdrawn) The method of claim 47, wherein the biodegradable polymer is selected from the group consisting of poly(lactides), poly(glycolide) copolymers of lactides, copolymers of glycolide, polyanhydrides, poly(hydroxyethyl methacylate), poly(imino carbonates), poly(N-acylhydroxyproline)esters, poly(N-palmitoyl hydroxyproline) esters, ethylene-vinyl acetate copolymers, poly(orthoesters), poly(caprolactones), and poly(phosphazenes).

49. (Withdrawn) The method of claim 42, wherein the polymeric resin has a density of from about 0.8 to about 3.0 g/cm^3.

50. (Withdrawn) The method of claim 44, wherein the core material of the grinding media is selected from the group consisting of zirconium oxides, zirconium silicate, glass, stainless steel, titania, alumina, and ferrite.

51. (Withdrawn) The method of claim 44, wherein the core material of the grinding media has a density greater than about 2.5 g/cm^3.

52. (Withdrawn) The method of claim 44, wherein the thickness of the polymeric resin coating on the core is from about 1 to about 500 microns.

53. (Withdrawn) The method of claim 44, wherein the thickness of the polymeric resin coating on the core is less than the diameter of the core.

54. (Withdrawn) The method of claim 30, comprising:

(a) continuously introducing particles of beclomethasone dipropionate and rigid grinding media into a milling chamber,

(b) contacting the beclomethasone dipropionate particles with the grinding media while in the chamber to reduce the particle size of the beclomethasone dipropionate particles;

(c) continuously removing beclomethasone dipropionate particles and the grinding media from the milling chamber, and

(d) separating the beclomethasone dipropionate particles from the grinding media.

55. (Withdrawn) The method of claim 30, comprising recirculating the beclomethasone dipropionate particles and the grinding media through the milling chamber.

56. (Withdrawn) The method of claim 30, comprising using grinding media having more than one particle size.

57. (Withdrawn) The method of claim 56, comprising at least two sizes of grinding media:

(a) having a mean particle size between about 1 and 300 mm; and

(b) having a mean particle size between about 300 and 1000 mm.

58. (Withdrawn) The method of claim 29, wherein the effective average particle size of the beclomethasone dipropionate particles is selected from the group consisting of less than about 1000 nm, less than about 400 nm, less than about 300 nm, and less than about 100 nm, meaning that at least 90% of the particles have a particle size less than the effective average.

59. (Withdrawn) The method of claim 58, wherein at least 95% of the beclomethasone dipropionate particles have a particle size less than the effective average.

60. (Withdrawn) The method of claim 58, wherein at least 99% of the beclomethasone dipropionate particles have a particle size less than the effective average.

61. (Withdrawn) The method of claim 29, wherein the surface modifier is present in an amount selected from the group consisting of from about 0.1% to about 90%, about 0.1% to about 75%, and about 20% to about 60%, by weight, based on the total combined weight of the beclomethasone dipropionate and surface modifier.

62. (Withdrawn) The method of claim 29, utilizing two or more surface modifiers.

63. (Withdrawn) The method of claim 29, wherein the surface modifier is selected from the group consisting of nonionic and ionic surfactants.

64. (Withdrawn) The method of claim 29, wherein the surface modifier is selected from the group consisting of gelatin, casein, lecithin, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxy propylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, tyloxapol, poloxamers, poloxamines, dextran, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonate, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)\text{-}CH_2(CHOH)_4(CH_2OH)_2$, decanoyl-N-methylglucamide, n-decyl-β-D-glucopyranoside, n-decyl-β-D-maltopyranoside, n-dodecyl-β-D-glucopyranoside, n-dodecyl-β-D-maltoside, heptanoyl-N-methylglucamide, n-heptyl-β-D-glucopyranoside, n-heptyl-β-D-thioglucoside, n-hexyl-β-D-glucopyranoside,

nonanoyl-N-methylglucamide, n-noyl-β-D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl-β-D-glucopyranoside, octyl-β-D-thioglucopyranoside, p-isononylphenoxypoly(glycidol), dioctylsulfosuccinate (DOSS), glycerol, dodecyl trimethyl ammonium bromide, a charged phospholipid, the triblock copolymer B20-3800, and the triblock copolymer B20-5000.

65. (Withdrawn) The method of claim 64, wherein the surface modifier is selected from the group consisting of block copolymers of ethylene oxide and propylene oxide, tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, a dioctyl ester of sodium sulfosuccinic acid, and dimyristoyl phophatidyl glycerol.

66. (Withdrawn) The method of claim 29, wherein the surface modifier is polyvinyl alcohol.

67. (Withdrawn) A method of making a nanoparticulate beclomethasone dipropionate composition comprising

(a) dissolving beclomethasone dipropionate in an aqueous base with stirring;

(b) adding the solution of beclomethasone dipropionate with stirring to a solution of one or more surface modifiers to form a clear solution;

(c) neutralizing the formulation from step (b) with stirring with an appropriate acid solution, and

(d) recovering particles of beclomethasone dipropionate having an average particle size of less than about 1000 nm.

68. (Withdrawn) The method of claim 67, further comprising removing any formed salt by dialysis or diafiltration.

69. (Withdrawn) The method of claim 67, further comprising concentrating the resulting beclomethasone dipropionate dispersion to a desired concentration of beclomethasone dipropionate.

70. (Withdrawn) The method of claim 67, wherein step (c) is carried out in semicontinuous, continuous batch, or continuous methods at constant flow rates of the reacting components.

71. (Withdrawn) The method of claim 67, further comprising dissolving a crystal growth modifier in step (a) with the beclomethasone dipropionate.

72. (Withdrawn) The method of claim 67, wherein the effective average particle size of the beclomethasone dipropionate particles is selected from the group consisting of less than about 1000 nm, less than about 400 nm, less than about 300 nm, and less than about 100 nm, meaning that at least 90% of the particles have a particle size less than the effective average.

73. (Withdrawn) The method of claim 72, wherein at least 95% of the beclomethasone dipropionate particles have a particle size less than the effective average.

74. (Withdrawn) The method of claim 72, wherein at least 99% of the beclomethasone dipropionate particles have a particle size less than the effective average.

EVIDENCE APPENDIX

The references cited herein were introduced into the record and entered during prosecution. Specifically, the only evidence discussed herein are the references forming the basis of the appealed rejection, which were cited in the Office Action mailed October 11, 2006.

RELATED PROCEEDINGS APPENDIX

Appellants are not aware of any related appeals or interferences, so Appellants have no information regarding related proceedings to submit.